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(71) Applicant *(for all designated States except US)*: GAMBRO AB [SE/SE]; Hamngatan 2, P.O. Box 7373, S–103 91 Stockholm (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: STERNBY, Jan [SE/SE]; Spårsnögatan 45, S–222 52 Lund (SE).

(74) Agent: ASKETORP, Göran; Gambro AB, Patent Dept., P.O. Box 10101, S–220 10 Lund (SE).

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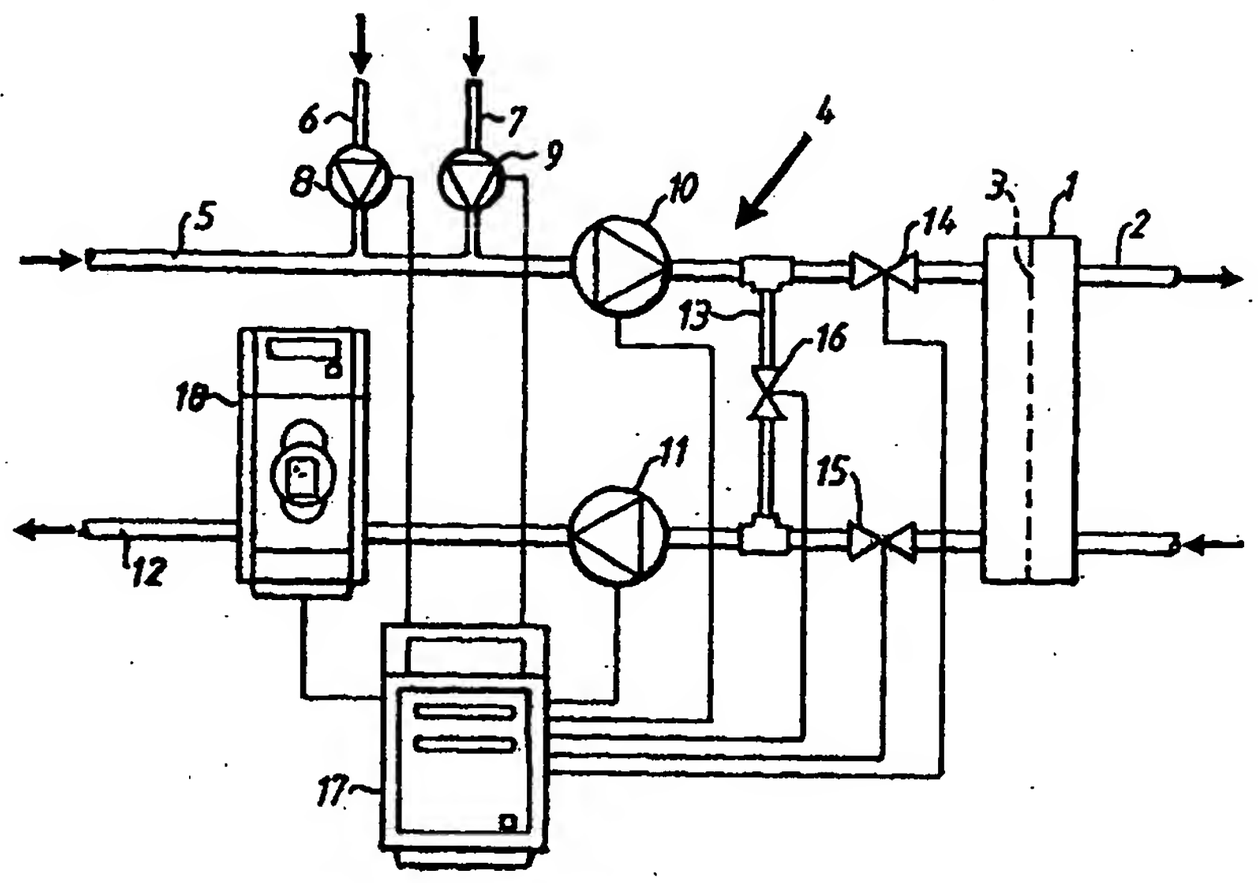

(57) Abstract

Method and apparatus for calculating the concentration of a substance in blood of a mammal. Blood from the mammal is passed through a dialyser having a semipermeable membrane and a dialysing fluid is passed at the other side of the membrane. The concentration of urea c_d is measured in the dialysate emitted from the dialyser and the dialysate fluid flow rate Q_d. A disturbance is introduced in the dialyser whereupon the effective dialysance K_e of the dialyser is calculated. Finally, the concentration of urea in blood is calculated by the formula $c_{pw} = c_d \times Q_d/K_e$. By using the curve of urea concentration c_d versus time in the dialysate, it is possible to calculate the initial mass m_0 of urea in the blood. Finally, the distribution volume V of urea in the body of said mammal is calculated according to the formula $V = m_0/c_{pw}$.

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TITLE: METHOD AND DEVICE FOR CALCULATING DIALYSIS EFFICIENCY

AREA OF THE INVENTION

The present invention relates to a method and device for calculating dialysis efficiency. More specifically, the invention relates to a non-invasive method and device for obtaining an initial concentration of urea and/or other solutes present in blood for further calculation of dialysis parameters.

The present invention is intended to be used during dialysis treatment, such as hemodialysis, hemodiafiltration or hemofiltration. It can also be used for peritoneal dialysis treatments. However, the invention is not limited to the above-mentioned treatment modes, but can also be used for other medical or non-medical purposes.

PRIOR ART

A method and device for calculating dialysis efficiency is disclosed in Swedish Patent Application No. 9702074-7 filed 1997-06-02, Applicant Gambro AB. In said Patent Application, a whole body relative efficiency is calculated. The calculation uses a removed urea concentration curve obtained by a urea monitor during dialysis treatment. The urea monitor measures the concentration of urea in the effluent fluid from the dialyser, normally emitted to the drain. The result obtained by the urea monitor is a value of the removed mass of urea m_{rem} as well as the removed urea concentration curve, from which can be calculated total accumulated urea mass m_0 in the body, whole body dialysis dose Kt/V, solute removal index SRI, etc.

It is, according to said Patent Application, required to obtain a value of the initial concentration of urea in blood in order to be able to fully characterise the dialysis treatment.

Another approach, also described, is to obtain a value of the total body water volume V of the patient, whereupon the urea concentration in the blood of the patient may be calculated.

A number of different approaches to obtain said initial concentration of urea are given in said Patent Application, like blood sample or equilibrated dialysis solution before the start of the treatment. These methods are more or less problematic and there is a desire to eliminate manual intervention. Moreover, blood samples need to be taken before the initiation of dialysis treatment. As soon as the treatment starts, the initial blood concentration of urea is diluted due to cardio-pulmonary recirculation and access recirculation. Thus, care must be exercised to obtain the initial urea concentration before it is compromised.

SUMMARY OF INVENTION

The object of the present invention is to provide a method and a device for obtaining the initial urea concentration in blood before the dialysis treatment, to be used in the invention according to Swedish Patent Application No. 9702074-7 for calculating essential dialysis related parameters of a patient.

Specifically, it is possible to use the total body urea mass m_0, obtained according to said Swedish Patent Application No. 9702074-7, and the initial urea concentration c_0 in blood obtained according to the present invention for calculating the distribution volume V of urea in the body. This parameter V is expected to be constant from the end of one treatment to the end of the next and could be used as an alternative to dry body weight as a parameter for determining the required ultrafiltration during a dialysis treatment. Moreover, the distribution volume V may be a long term marker for the general status of the patient.

A method of determining the dialysance of a dialyser used during dialysis treatment is disclosed in EP 658 352 filed by Hospal AG. According to this method, a disturbance is generated in the fresh dialysis solution before the dialyser and the resultant effect in the dialysate after the dialyser is

measured. Normally, the disturbance is induced in the conductivity of the dialysis solution. The method gives the effective ionic dialysance for the dialyser and the effective plasma conductivity.

In clinical studies this ionic dialysance for a dialyser measured according to EP 658 352 has been shown to agree well with the effective plasma water clearance of that dialyser for urea (K_e), i.e. plasma water clearance corrected for recirculation, pulmonary recirculation as well as access recirculation.

The definition of clearance implies that the urea mass removal rate equals the product of the effective plasma water clearance (K_e) and plasma water concentration (c_{pw}) of urea in the systemic blood returning from the body. The difference between dialyser clearance and effective dialyser clearance is that for dialyser clearance the denominator should be plasma water concentration in the blood entering the dialyser while for effective dialyser clearance the denominator should be plasma water concentration in the systemic blood returning from the body. Due to recirculation this concentration in the blood entering the dialyser differs from the concentration in the systemic blood returning from the body.

The urea mass removal rate is measured by the urea monitor as the product of dialysate flow rate (Q_d) and the urea concentration in the spent dialysate (c_d). We can therefore equate the two expressions for urea mass removal rate from plasma water and into the spent dialysate

$$K_e \times c_{pw} = Q_d \times c_d$$

In this equation, K_e may be obtained by the method of EP 658 352 or a similar method, while Q_d and c_d are obtained by the urea monitor. Thus, c_{pw} can be calculated.

There is, however, an additional effect that has to be taken into account. Due to internal resistance in the body to urea transport, a urea gradient starts to develop within the body from the start of a dialysis treatment. This means that the urea concentrations in different parts of the body are

gradually differing more and more, and the urea concentration in the blood returning from the body, which is used in the calculations above, is no longer representative of the mean urea concentration in the body. It is therefore only before or at the initiation of a treatment, while urea is equally distributed in the body, that the calculation above can be used to find the mean urea concentration in the body.

The urea monitor is programmed to find the starting value for dialysate urea c_{d0} by interpolating backwards along the concentration curve using measurements from 20 to 5 minutes after the treatment start time, which is defined as the time when the measured dialysate urea concentration c_d is steadily above a predetermined low concentration value. Due to time constants in the monitor this starting value will not catch the initial decrease in urea due to the development of recirculation, so this initial dialysate urea concentration c_{d0} will be representative of conditions with recirculation already developed. Using this starting value of c_d in the formula above, together with a measurement of effective clearance (K_e) performed by for example the method described in EP 658 352, will produce the initial plasma water concentration c_{pw0} of urea in the blood returning from the body. At the start, before any gradients have developed in the body, this will also be the mean plasma water concentration in the body. The measurement of effective clearance K_e should preferably be performed as soon as possible after the initial 20 minutes (for the interpolation of initial dialysate urea) to avoid unintentional changes in clearance, and all factors affecting clearance such as blood and dialysate flows should be kept constant during this period.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic view of a dialysis machine intended for hemodialysis including a urea monitor and where the invention can be used.

Fig. 2 is a schematic view similar to Fig. 1, but with the urea monitor integrated in the dialysis machine.

Fig. 3 is a schematic view similar to Fig. 1 of a dialysis machine adapted for predilution hemofiltration.

Fig. 4 is a schematic view similar to Fig. 2 of a dialysis machine adapted for postdilution hemofiltration.

Fig. 5 is a diagram over concentration values obtained from the urea monitor in the dialysis machine according to anyone of Figs. 1 - 4.

DESCRIPTION OF PREFERRED EMBODIMENTS

Fig. 1 is a schematic diagram of a dialysis machine in which the invention according to Swedish Patent Application No. 9702074-7 and the present invention can be practised. The dialysis machine provides means for replacing the renal function of a mammal if the renal function is impaired or completely absent, such as end stage renal disease of a human being.

The blood from a patient is taken out into an extracorporeal circuit 2 including a filter or dialyser 1, including a semipermeable membrane 3. The blood passes along one side of the membrane. At the other side of the membrane, a dialysis fluid is circulated by the dialysis machine 4.

The dialysis fluid is usually prepared by the machine from one or several concentrates and water to form a dialysis fluid having the desired properties. Thus, the machine disclosed in Fig. 1 comprises a water inlet 5, two concentrate inlets 6 and 7, and two concentrate metering pumps 8 and 9. A first main pump 10 propels the fresh dialysis fluid to the dialysis side of the dialyser into contact with the membrane.

A second main pump 11 passes the effluent fluid, dialysate, from the dialyser, namely the inlet dialysis fluid and any ultrafiltrate removed from the blood via the filter, further on to an outlet 12 and to the drain.

A by-pass line 13 is arranged between the first pump 10 and the second pump 11. Several valves 14,15,16 are arranged for controlling the flow of dialysis fluid. The valves and the pumps are controlled by a computer 17 as schematically shown by several lines in Fig. 1. Of course, the dialysis machine is provided with several other means as is conventional. These other means are not disclosed, since they are conventional.

The first main pump 10 is driven with a speed so that the dialysis fluid delivered to the dialyser is substantially constant, e.g. 500 ml/min. The second main pump 11 is driven with a slightly higher speed so that the effluent fluid, called the dialysate, has a flow rate of e.g. 515 ml/min. This operation generates a low pressure at the dialysate side of the dialyser, which is suitable for removing 15 ml/min of ultrafiltrate fluid from the blood, i.e. plasma water. During a treatment of 4 hours, such ultrafiltration results in a fluid removal from the patient of 3,6 litres. Of course, the dialysis machine is operated so that the treatment prescribed to the patient is fulfilled.

In the effluent line from the dialysis machine is placed a urea monitor 18, which measures the urea concentration c_d in the effluent dialysate. The monitor can be positioned inside the dialysis machine or completely outside the dialysis machine. The urea monitor may be of the type disclosed in WO 96/04401.

The urea monitor is shown connected to the computer 17 of the dialysis machine. However, the monitor may have a computer of its own.

The urea monitor or the dialysis machine also includes means for measuring the flow rate of the effluent dialysate, Q_d. The computer 17 is arranged to provide concentration values c_d as well as values of the total mass of urea U removed during the treatment as the integral of $Q_d \cdot c_d$. The concentration values are taken continuously so that a concentration curve c_d is obtained from the urea monitor as well as a mass curve U.

Fig. 2 discloses a similar dialysis machine as shown in Fig. 1. The main difference is that the urea monitor 19 is placed between the dialyser 1 and the second main pump 11 and before the outlet of the bypass line.

Fig. 3 discloses a similar dialysis machine as Fig. 1, but adapted for hemofiltration or hemodiafiltration. The only difference is that there is included an infusion line 20 including an infusion pump 21. The infusion line 20 starts from the outlet of the first main pump 10 and ends at the blood inlet side of the dialyser, for providing an infusion fluid to the blood before the dialyser, called predilution. The urea monitor

22 is arranged in the effluent dialysate line after the second pump 11.

Fig. 4 discloses a similar dialysis machine as Fig. 2, but adapted for hemofiltration or hemodiafiltration and providing an infusion fluid to the blood after the dialyser, called postdilution. The urea monitor 23 is placed before the second main pump 11 and before the outlet of the bypass line.

Finally, Fig. 5 discloses a typical urea concentration curve c_d obtained from the urea monitor. As appears from the figure, the curve is very irregular and includes several dips. These dips reflect when the dialysis machine is connected for selfcalibration, in which valve 16 is opened and valves 14 and 15 are closed.

For the operation of the invention according to Swedish Patent Application No. 9702074-7, please refer to that application, which is included herein by reference. The result is that the urea monitor provides a removed urea concentration curve c_d as disclosed in Fig. 5. The initial values, for example values obtained from 5 minutes to 20 minutes, are used for extrapolating an initial urea concentration c_{d0} at the start of the dialysis treatment.

The start of the dialysis treatment is defined as the time when the urea concentration is steadily above a predetermined low concentration value. The actual determination of concentration values is initiated five minutes after determining such a steady condition in order to be sure that the treatment is going on and will not be discontinued.

In order to obtain a measurement of the effective dialyses of the dialyser, a disturbance is induced in the fresh dialysate by operating the pumps 8 and 9 controlled by the computer 17. The disturbance is generated when the dialysis treatment is in a steady state and may be a change in the ionic content of the dialysis fluid. Such a disturbance may be generated by operating both pumps 8 and 9 and increase the speed of these pumps by for example 10% during 60 seconds.

The resultant disturbance is measured after the dialyser, for example by a conductivity meter, and the measurement result is processed for example as described in

EP 658 352 to obtain the effective dialysance K_e. The measurement is performed as soon as possible and preferably after the initial 20 minutes and without changing any of the parameters influencing on the dialysance of the dialyser, like blood flow rate and dialysate flow rate. EP 658 352 is incorporated in the present application by reference.

If the disturbance is a step change in the conductivity, produced by pumps 8,9 the dialysance of the dialyser can be determined according to equation (see EP 547 025, the contents of which is included in the present application by reference):

$$D_e = Q_d \left[1 - (C_{dout2} - C_{dout1}) / (C_{din2} - C_{din1})\right]$$

where

D_e = effective dialysance of the dialyser

Q_d = effluent dialysate flow

C_{dout1} and C_{dout2} = concentration in the effluent dialysate

C_{din1} and C_{din2} = concentration in the introduced dialysis fluid

The concentrations may be sodium concentrations or conductivity of the dialysate.

Indexes 1 and 2 indicate times before and after the step change. The introduced concentration can be measured before the dialyser or be determined by the set values of the concentration pumps.

The value of the effective dialysance is used for determining the initial urea concentration in blood at the start of the treatment according to the formula:

$$C_{pw0} = Q_d \times C_{d0} / K_e$$

The plasma urea concentration can then be corrected for protein content in the blood. This correction is fairly constant for the normal range of protein concentrations, which allows the use of the same correction factor for all patients, although the best accuracy is achieved if the true protein content is used.

It is noted that the urea monitor includes a conductivity meter, which may be used for measuring the conductivity after the dialyser, so there need not be any

separate conductivity meter after the dialyser for the measurement according to the present invention.

Instead of measuring the conductivity before the dialyser, the set values of the disturbance can be used.

The disturbance may be induced in different manners.

One approach is to use a small dose of urea, which is introduced in the fresh dialysis fluid just before the entrance into the dialyser as disclosed in Fig. 2. A pump 24 is connected to the inlet of the dialyser downstream of valve 14. The pump is also connected to a small bag 25 containing a predetermined quantity of urea dissolved in water or dialysis fluid (or an isotonic solution) and having a predetermined concentration.

The disturbance induced by this introduction of the known amount of urea in the dialysis circuit is measured by the urea monitor downstream of the dialyser and the result is evaluated by the computer 17. By integrating the measured urea concentration due to the disturbance, the mass of urea reaching the urea monitor can be calculated by multiplication with the flow rate Q_d. The difference from the amount introduced, which is known, must have passed through the membrane of the dialyser into the blood of the patient. Thus, the effective dialysance D_e or the effective clearance K_e for urea of the dialyser can be calculated, according to the formula:

$$D_e = Q_d \times (1 - S_{out}/S_{in})$$

where:

D_e = effective dialysance of the dialyser

Q_d = dialysate flow emitted from the dialyser

S_{out} = integral of (cd(t) - cd0) during the disturbance in the flow emitted from the dialyser

S_{in} = integral of (cd(t) - cd0) during the disturbance in the flow entered into the dialyser

The best accuracy is obtained if the dialysate flow Q_d is constant, i.e. that the flow rate is compensated for the fluid added to the inlet of the dialyser as indicated more in details below.

Of course, the bag 25 may include sodium ions instead of urea and the conductivity meter of the urea monitor may be used for measuring the increased conductivity due to the introduction of extra sodium ions. It is known that the clearance for sodium ions is approximately equal to the clearance of urea. Other types of ions or substances can also be used as well as decreases instead of increases of the concentration or conductivity of the fresh dialysis solution.

If pure water is added, i.e. water without any ions or other substances, the integral given above will be negative, and the surface will have a relationship with the amount of added water.

It is noted that the integral S_{in} times the dialysis fluid flow equals the amount of material added to the solution. Thus, if urea is added, S_{in} need not be measured but can be calculated from the known amount of urea and the dialysis fluid flow. Possibly, a correction for dilution is required.

The same applies if sodium is used, whereby $S_{in} \times Q_{din}$ equals the addition of material in excess of the normal amount, which normally is known in advance.

It is also apparent that the material can be added in any way that enables the measurement at the outlet side of the dialyser, i.e. the disturbance need not be rectangular, but can have any shape. Thus, the introduction flow rate of the material in the dialysate flow is of no importance as soon as it is of such a flow rate that the resultant disturbance is not too small to be measured and not to large to be outside the measuring capability of the measurement instrument at the outlet side of the dialyser. Of course, the disturbance must also be compatible with the body.

The added material can be dissolved in water, whereby the dilution effect should be considered when introducing the material in the circuit. Another approach would be to dissolve the material in normal dialysis fluid, for example dissolve a known amount of urea in a known amount of dialysis fluid. This dissolution can be performed in advance, so that the material is delivered in bag 25 to be connected to the dialysis circuit. Alternatively, the material can be delivered in powder form, for

example a known amount of urea in powder form in a bag 25. The bag is connected to the dialysis machine, and the pump 24 is operated to introduce a known amount of dialysis fluid in the bag to dissolve the amount of material. After dissolution, the pump 24 is reversed and the material in the bag is introduced into the circuit.

The main pump 16 can be operated so that the total amount of fluid entering the dialyser is constant, i.e. the flow rate of pump 16 and pump 24 is constant. For example, if pump 24 is operated at a speed of 50 ml/min, pump 16 is reduced to 450 ml/min during the introduction period and returned to 500 ml/min after the introduction of the substance.

Alternatively, the disturbance may be introduced at the other side of the membrane as suggested in Fig. 2 by pump 26 and bag 27. In the same way as with pump 24 and bag 25, an introduction of urea of a known concentration and/or amount will result in an increase of the urea concentration in the dialysate reaching the urea monitor. This disturbance can be integrated and processed for obtaining the clearance of the dialyser.

The added material can be fresh dialysis fluid obtained from the dialysis machine, but of a higher (or lower) ionic strength or osmolarity, whereby the conductivity is measured. Alternatively, fresh dialysis fluid can be added, which comprises no urea, and the resulting diluting effect on urea in blood can be determined on the dialysate side by the urea monitor.

The added material, such as urea can be diluted in water or dialysis fluid as indicated above. Moreover, the material can be delivered in powder form in a bag 27 and dissolved in blood by reversing pump 26 and introducing blood in the bag for dissolution of the material and then operating the pump 26 in the normal direction for introducing the material in the circuit.

The time of the measurement may be shortened by using the exponential behaviour of the disturbance for calculating the result as stated in EP 658 352.

When using the integral method, the time may be shortened in the same way by estimating the error when the measurement is terminated in advance.

Hereinabove, the invention has been described in details by means of several embodiments of the invention. The different features in the different embodiments can be combined in further different ways, which combinations are intended to be within the scope of the present invention. The invention is only limited by the appended patent claims.

PATENT CLAIMS

1. Method of calculating the concentration of a substance in blood of a mammal

passing the blood through a dialyser comprising a semipermeable membrane and passing a dialysing fluid at the other side of the membrane;

measuring the concentration c_d of said substance in said fluid emitted from said dialyser;

characterised by

introducing a disturbance in said dialyser and calculating the effective dialysance K_e of said dialyser; and

calculating the concentration c_{pw} of said substance in blood.

2. Method according to claim 1, **characterised** by

obtaining the dialysate fluid flow rate Q_d and calculating the concentration of said substance in blood by the formula

$$c_{pw} = c_d \times Q_d / K_e$$

3. Method according to claim 2, **characterised** by

measuring the concentration c_d of said substance in said fluid to obtain a curve over the concentration versus time;

calculating the initial mass m_0 of said substance in the blood;

calculating the initial concentration c_{pw0} of said substance in the body, e.g. by extrapolating to an initiation time;

calculating the distribution volume V of said substance in the body of said mammal according to the formula

$$V = m_0 / c_{pw0}$$

4. Method according to claim 1, 2 or 3, **characterised** by

calculating the effective dialysance K_e of said dialyser by introducing a disturbance in said dialyser in the nature of a change of the concentration of a second substance in said dialysis fluid introduced in the dialyser;

measuring the resulting change in the concentration of said second substance in said dialysis fluid leaving the dialyser for calculating the effective dialysance K_e of said dialyser.

5. Method according to claim 1, 2 or 3, **characterised** by introducing a known amount of a substance ($m_{urea\ in}$) into the dialysis fluid entering the dialyser;

measuring the concentration (c_d) of said substance in the dialysate emitted from the dialyser;

multiplying the concentration (c_d) with the dialysate flow (Q_d) and integrating the product versus time to obtain an amount ($m_{urea\ out}$) of said substance at the outlet of the dialyser;

calculating the effective dialysance K_e of said dialyser by the formula:

$$D_e = Q_d \times (1 - m_{urea\ out} / m_{urea\ in})$$

where:

D_e = effective dialysance of the dialyser

Q_d = dialysate flow emitted from the dialyser.

6. Method according to claim 4 or 5, **characterised** in that the first substance is urea and the second substance is sodium ions, conductivity or urea.

7. Apparatus for calculating the concentration of a substance in blood of a mammal, comprising:

means for passing the blood through a dialyser comprising a semipermeable membrane and means for passing a dialysing fluid at the other side of the membrane,

means for measuring the concentration c_d of said substance in said fluid emitted from said dialyser,

characterised by

means for introducing a disturbance in said dialyser and for calculating the effective dialysance K_e of said dialyser; and means for calculating the concentration c_{pw} of said substance in blood.

8. Apparatus according to claim 7, **characterised** by means for obtaining the dialysate fluid flow rate Q_d and for calculating the concentration of said substance in blood by the formula

$$c_{pw} = c_d \times Q_d / K_e$$

9. Apparatus according to claim 8, **characterised** by

means for measuring the concentration c_d of said substance in said fluid to obtain a concentration curve;

means for calculating the initial mass m_0 of said substance in the body,

means for calculating the initial concentration c_{pw0} of said substance in the body, e.g. by extrapolating to an initiation time; and

means for calculating the distribution volume V of said substance in the body of said mammal according to the formula

$$V = m_0 / c_{pw0}$$

10. Apparatus according to claim 7, 8 or 9 **characterised** by

means for calculating the effective dialysance K_e of said dialyser by introducing a disturbance in said dialyser in the nature of a change of the concentration of at least a second substance in said dialysis fluid introduced in the dialyser;

means for measuring the resulting change in the concentration of said second substance in said dialysis fluid leaving the dialyser, and

means for calculating the dialysance of said dialyser.

11. Apparatus according to claim 7, 8 or 9, **characterised** by

means for introducing a known amount of a substance ($m_{urea\ in}$) into the dialysis fluid entering the dialyser;

means for measuring the concentration (c_d) of said substance in the dialysate emitted from the dialyser;

means for multiplying the concentration (c_d) with the dialysate flow (Q_d) and integrating the product versus time to obtain an amount ($m_{urea\ out}$) of said substance at the outlet of the dialyser;

means for calculating the effective dialysance K_e of said dialyser by the formula:

$$D_e = Q_d \times (1 - m_{urea\ out} / m_{urea\ in})$$

where:

D_e = effective dialysance of the dialyser

Q_d = dialysate flow emitted from the dialyser.

12. Apparatus according to claim 10 or 11, **characterised** in that the first substance is urea and the second substance is sodium ions, conductivity or urea.

Fig.1

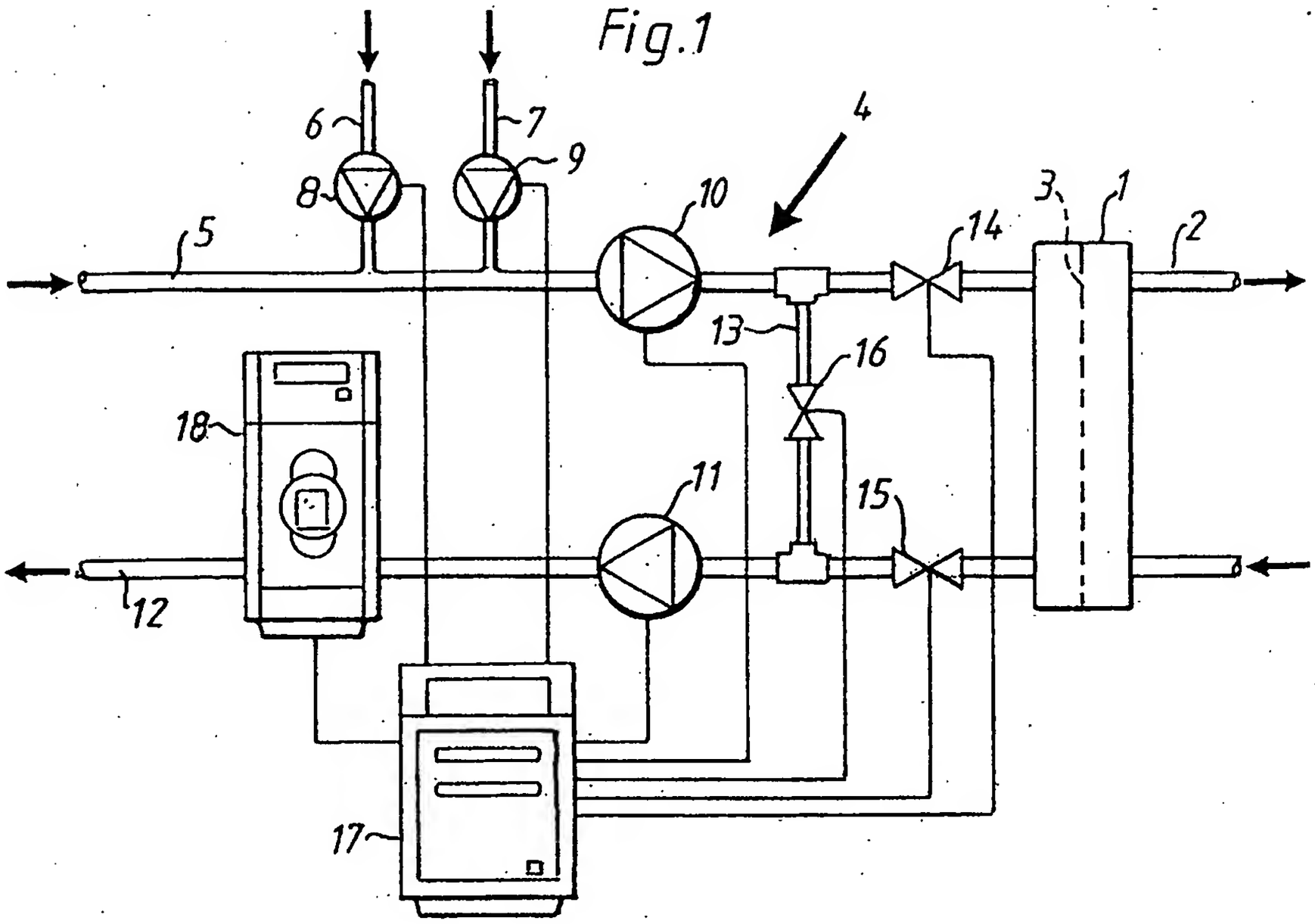
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Fig.2

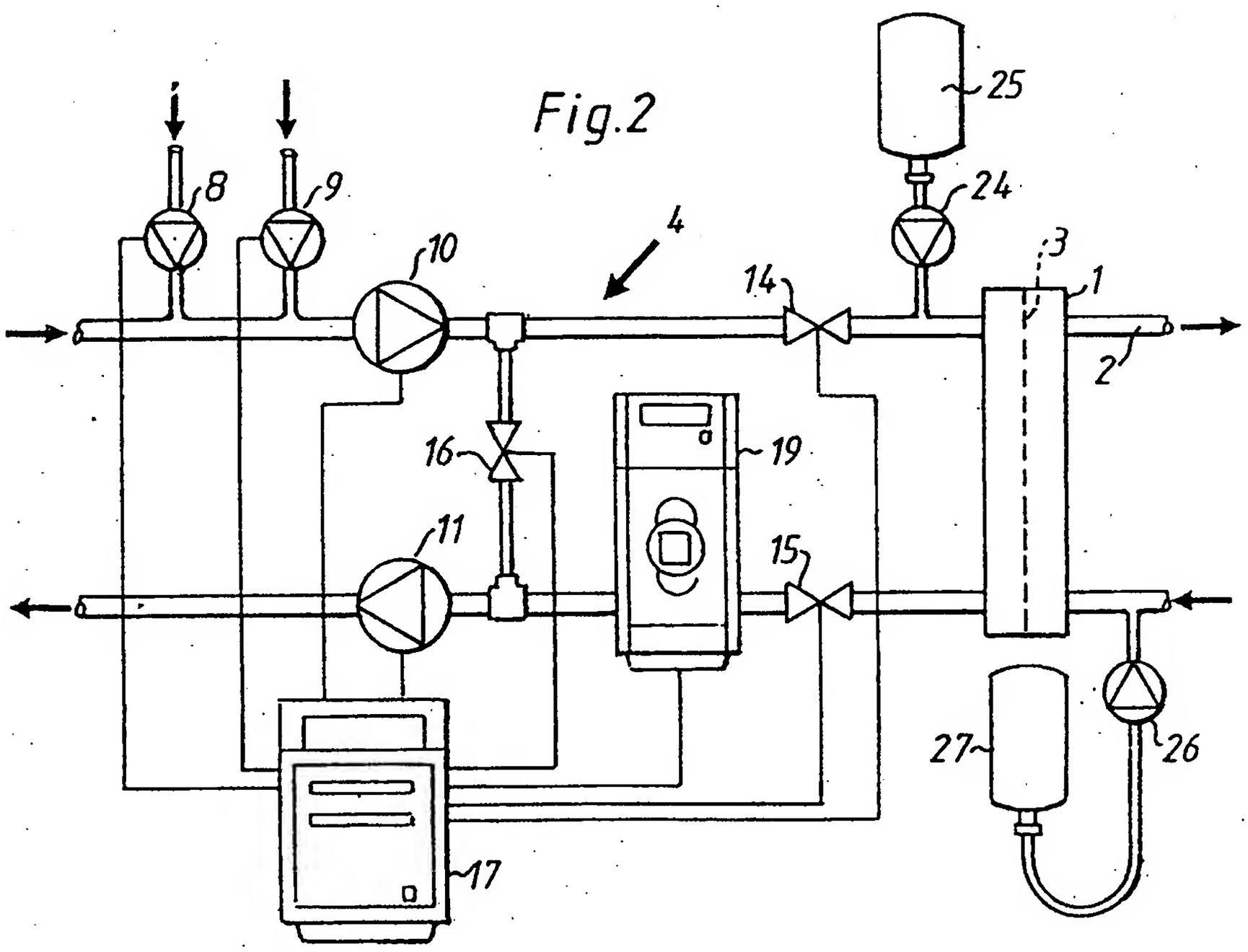
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Fig.3

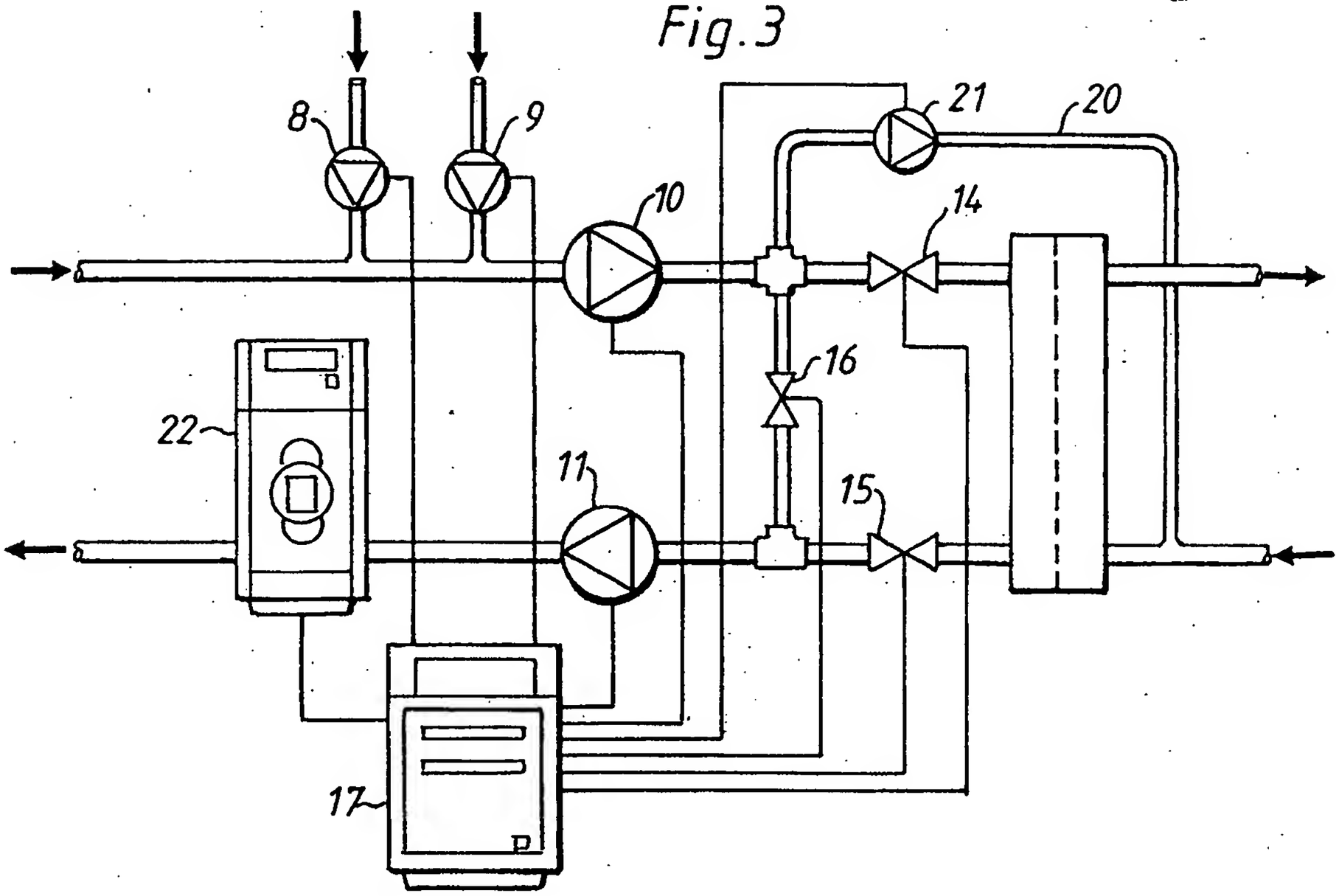


Fig.4

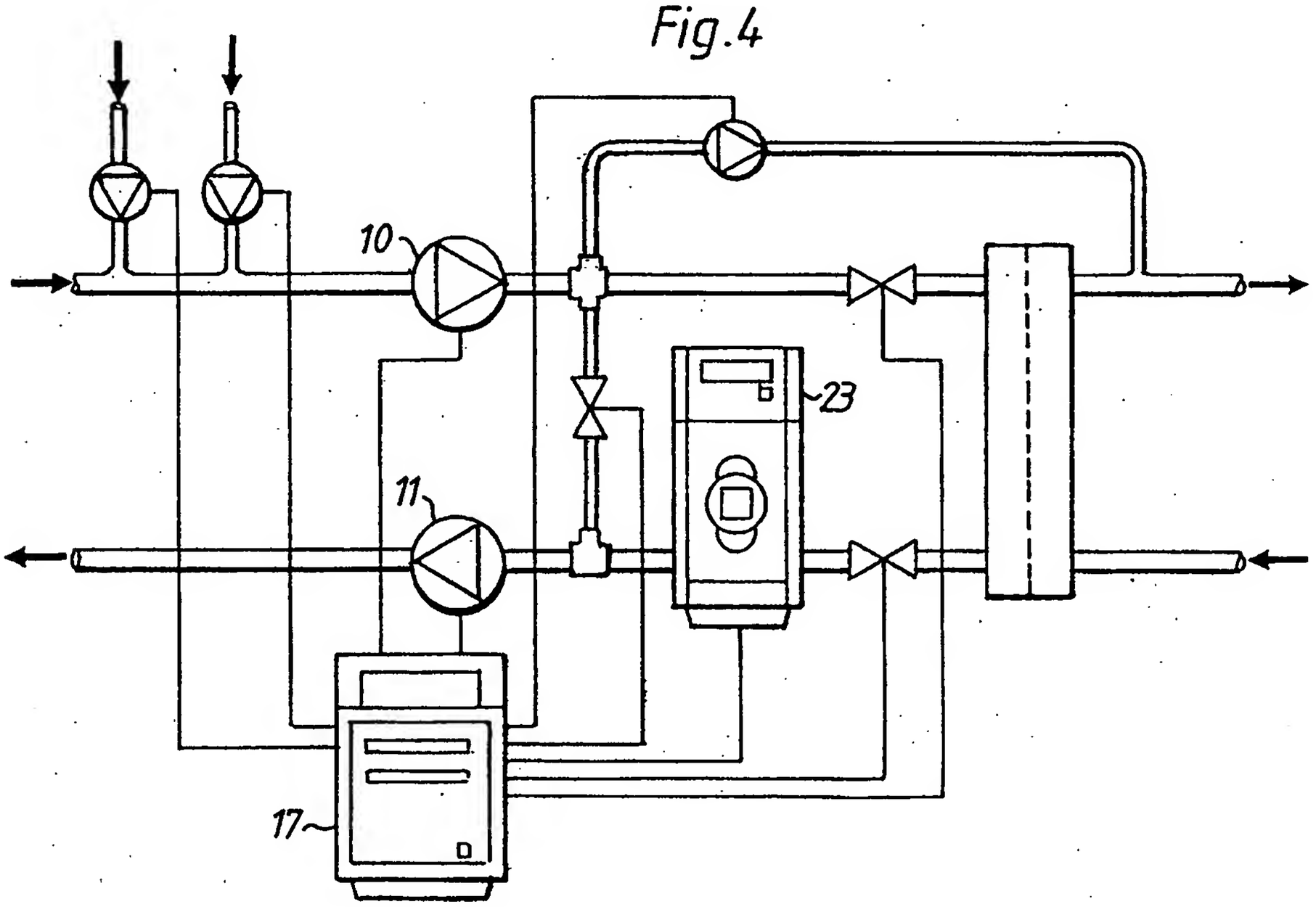
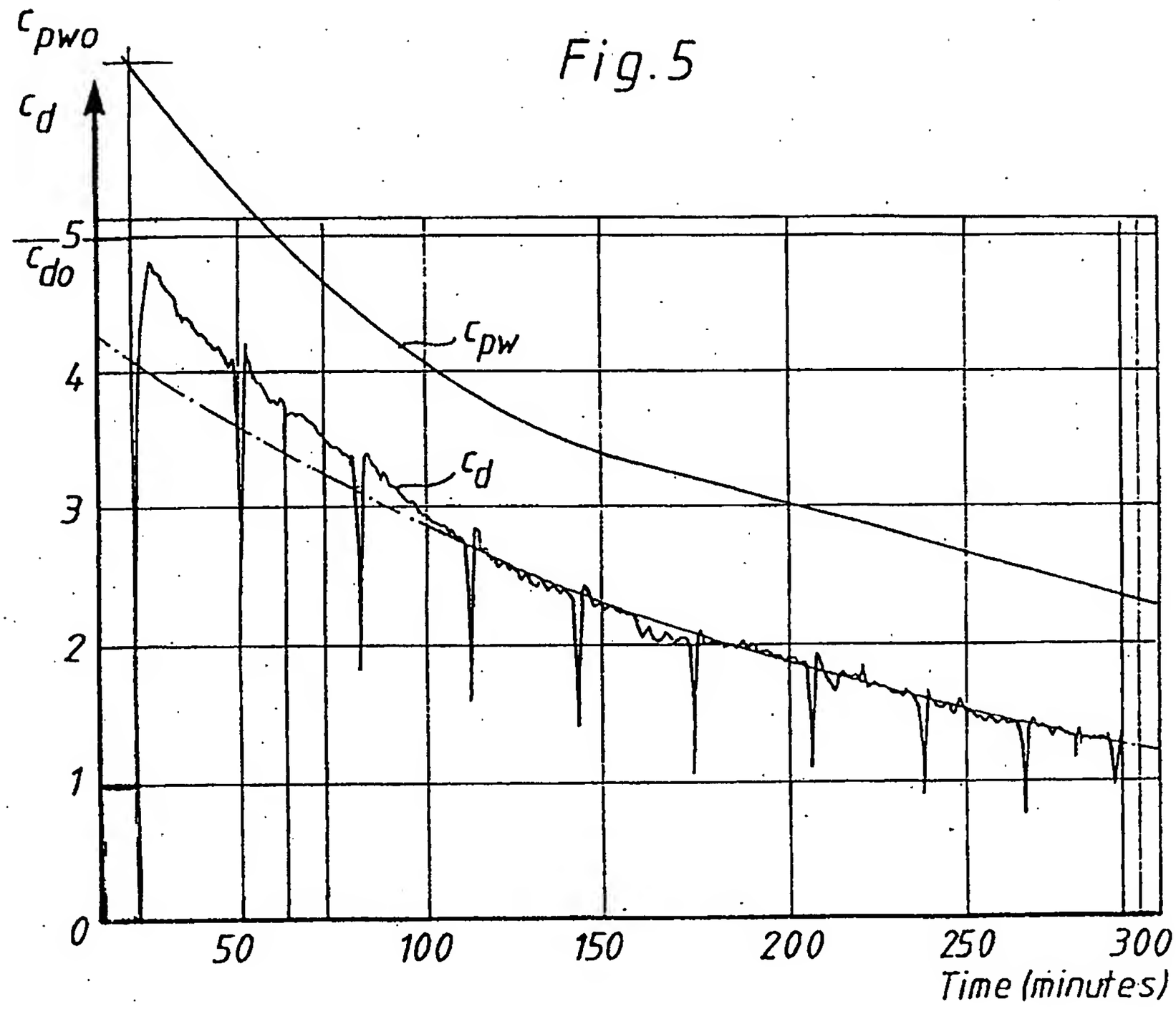


Fig.5



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02212

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61M 1/14, G01N 33/487
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61M, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5567320 A (NICOLAS GOUX ET AL), 22 October 1996 (22.10.96), column 7, line 47 - line 59	1-3,5-9, 11-12
A	--	4,10
A	US 5644240 A (JAMES M BRUGGER), 1 July 1997 (01.07.97), abstract	1-12
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A	WO 9532010 A1 (BAXTER INTERNATIONAL INC.), 30 November 1995 (30.11.95), abstract	1-12
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A	US 5100554 A (HANS-DIETRICH POLASCHEGG), 31 March 1992 (31.03.92), abstract	1-12
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 1999	10 -03- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Malin Keijser Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/02/99

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